Single Technology Appraisal

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Contents:

The following documents are made available to stakeholders:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]: Decision of the panel

Introduction

1. An appeal panel was convened on 27 April 2023 to consider an appeal against NICE's final appraisal document, to the NHS, on daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748].

2. The appeal panel consisted of:

• Professor Jonathan Cohen	Chair
• Alina Lourie	Non-executive director
• Dr Biba Stanton	Health service representative
• Dr Rachel Russell	Industry representative
• David Chandler	Lay representative

3. None of the members of the appeal panel had any competing interest to declare.

4. The panel considered appeals submitted by Janssen and Myeloma UK.

5. Janssen was represented by:

• Dr Margaret Wan	Medical lead, Haematology
• Amanda Cunnington	Senior Director, Patient Access
• Nicola Trevor	Director of Health, Economic, Market Access and Reimbursement

- Andrew Ternouth — Head of Health, Economic, Market Access and Reimbursement
- Dr Adela Williams — Legal Representative

6. Myeloma UK was represented by:

- Shelagh McKinlay — Director of Research and Advocacy
- Professor Ashutosh Wechalekar — Consultant Haematologist
- Dr Mamta Garg — Consultant Haematologist
- Michael Jameson — Patient representative
- Sarah Love — Legal representative

7. In addition, the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

- Dr Charles Crawley, chair — Technology appraisal committee B
- Baljit Singh, vice chair — Technology appraisal committee B
- Henry Edwards — Associate Director, technology appraisals, NICE
- Yelan Guo — Technology assessment adviser, NICE

8. The appeal panel's legal adviser Amy Smith was also present.

9. Under NICE's appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.

10. There are two grounds under which an appeal can be lodged:

Ground one: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

Ground two: The recommendation is unreasonable in light of the evidence submitted to NICE.

11. Dr Mark Chakravarty, NICE's lead non-executive director for appeals, in preliminary correspondence had confirmed that:

- Janssen had potentially valid grounds of appeal as follows: Grounds 1a and 2
- Myeloma UK had potentially valid grounds of appeal as follows: Grounds 1a and 2

12. The appraisal that is the subject of the current appeal provided advice to the NHS on daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748].

13. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: Amanda Cunnington on behalf of Janssen, Sarah Love and Michael Jameson on behalf of Myeloma UK and Dr Charles Crawley on behalf of the appraisal committee.

14. The appeal panel were very grateful for Michael Jameson's eloquent and moving description of his experience as a patient with this condition.

15. The remainder of this document sets out the panel's decisions in the following order:

a. Janssen's ground 1a points;

b. Myeloma UK's ground 1a points;

c. Janssen's ground 2 points; and

d. Myeloma UK's ground 2 points.

Appeal by Janssen

Appeal Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly

Appeal Ground 1a.1: The appraisal committee has failed to take into account factors other than uncertainty when defining the ICER threshold for this appraisal.

16. This appeal point was considered alongside Myeloma UK appeal point 1a.4 at the hearing, so the following should be read in conjunction with that section of this decision letter. In determining this point 1a.1 the panel had regard to the full discussion at the hearing in relation to this point and Myeloma UK appeal point 1a.4.

17. Nicola Trevor, for Janssen, stated that paragraph 3.20 of the final appraisal document (FAD) says that the high level of uncertainty led the committee to conclude that an acceptable ICER would be well below £30,000. She stated that amyloid light-chain (AL) amyloidosis is an "ultra-rare" condition and that such a low ICER threshold is completely at odds with the flexibility afforded by the highly specialised technologies (HST) programme. She acknowledged that the FAD refers to the severity of the condition, unmet need, the potential uncaptured benefits and the innovative nature of the technology in different places. However, where the ICER threshold is discussed at paragraph 3.20, the only factor mentioned as a rationale for the ICER threshold is uncertainty. She said it is therefore unclear how these other factors were taken into account. She submitted it is procedurally unfair not to give adequate consideration to these other factors or – if such consideration was given – to give an adequate explanation in the FAD of how.

18. Henry Edwards, for NICE, said that there was an editorial error in the FAD. The strapline for paragraph 3.20 should have been but was not updated from the appraisal consultation document (ACD) and was incorrect in stating that "an acceptable ICER threshold is £20,000 per QALY gained". The statement in the body of the paragraph that an acceptable ICER would be "well below £30,000 per QALY gained" was the correct one. He referred to 6.3.1 of NICE's Guide to the methods of technology appraisal 2013 and explained NICE has a duty to consider the opportunity cost of approving a technology.

He drew attention to the places in the FAD where innovation and potential additional benefits of daratumumab are mentioned. He said that the rarity of AL amyloidosis and the unmet need for treatments were considered at the committee meetings and are mentioned in the slides. He said that even having considered uncertainty, uncaptured benefits and rarity, the committee still could not recommend daratumumab. He said that the change in the ICER threshold between the ACD and the FAD demonstrated that the committee had given further consideration to the factors mentioned by the appellants. He also said that the committee had not been provided with any ICER within the range normally considered an acceptable use of NHS resources.

19. In response to questions from the panel, Henry Edwards acknowledged that rarity was not mentioned in the FAD. He referred to section 6.2.16 of the methods guide that refers to evidence necessarily being weaker for a rare disease. In fact, in this case Janssen described the evidence as “robust” and the committee judged that this was by no means the weakest evidence they have seen in the context of rare diseases.

20. Dr Charles Crawley, for NICE, said that the main issue regarding rarity is how it impacts on the evidence: if appraising a treatment for a very rare condition with little evidence to support it, the committee are mindful not to penalise those with the condition because it is not possible to provide the usual standard of evidence. He stated that the committee understood that AL amyloidosis is a rare condition. However, he agreed that the evidence provided was quite impressive, so the rarity of the condition did not appear to have impacted on the ability to provide evidence.

21. In response to questions from the panel noting that innovation is referenced at paragraph 3.19 of the FAD, Dr Adela Williams, for Janssen, said that the issue is not only whether the committee considered additional factors in determining the ICER threshold but how they took them into account in their analysis. She acknowledged that it is clear the committee knew about the degree of clinical need and rarity of AL amyloidosis, but it was not clear how these factors were taken into account in setting the cost-effectiveness threshold. She submitted that the ICER threshold was set so low that it was almost impossible for a treatment for such a rare disease to meet it. Taking

into account the rarity of AL amyloidosis along with unmet need and innovation, it was hard to understand how the committee could ever have suggested a £20,000 per Quality Adjusted Life Year (QALY) ICER threshold.

22. In response to questions from the panel, Nicola Trevor said that rarity is important and should lead to more flexibility around uncertainty because it makes it challenging to generate evidence, and the fact that companies have to invest more to generate evidence in a rare disease. The degree of clinical need in this case arises from the fact that there is no other licensed treatment for this severe, life-threatening condition.

23. Henry Edwards said that the committee considered that an acceptable ICER threshold would be well below £30,000. The committee are asked to determine an ICER threshold for what ICERs they would be willing to consider an acceptable use of NHS resources. He said that the committee are asked to take a deliberative rather than quantitative approach when considering most plausible ICERs against that threshold in any given appraisal. In this case the committee did not see any ICERs below £30,000, so they could not consider something that was not on the table. If they had, it would have been a more challenging decision. They did not set a strict threshold of £20,000 but after taking everything into account felt that it could not be as high as £30,000. If there had been an ICER within the range of £20,000 to £30,000 it would have been something the committee could deliberate on. In response to the appellant's comments about transparency, he said that the FAD is trying to summarise many pages of documents over a long appraisal process. He agreed that there had to be enough information for a reader to understand the decision making, and said the committee would be happy to edit the FAD if needed.

24. Dr Charles Crawley reiterated that the committee considers ICERs presented to them and asks itself whether these are plausible and whether there is one within a cost-effective range. While the committee must determine an acceptable ICER threshold/range for the purpose of considering the ICERs put to them, the ICER threshold is not fixed and is always up for discussion if for example the evidence changes. In this appraisal, the committee did not see an ICER within an acceptable range.

25. Dr Adela Williams said that she was puzzled by the statement that no cost-effective ICERs had been presented as this was not her understanding.

26. Henry Edwards confirmed that the committee had not seen ICERs in the cost-effective range once confidential discounts for the competitor products had been applied. The lower end of the ICER range was £34,000 but the upper end was considerably higher.

27. Nicola Trevor said that the editorial error in the FAD that stated an acceptable ICER threshold was £20,000 had impacted on the company's ability to consider a managed access arrangement. This threshold would have set the bar ridiculously high.

28. Henry Edwards said that the editorial error in the FAD would have been corrected as part of factual accuracy checking before the FAD was published and would have been corrected in any commercial discussions with NHS England. He stated that for a technology to enter the cancer drugs fund there has to be a plausible ICER below £30,000 which was not the case here.

29. The appeal panel concluded as follows. The panel accepted that the committee had been aware of the rarity of AL amyloidosis, the unmet clinical need in this condition and the potential for benefits that were not fully captured in the model, and that this was clear from the papers. However, the panel was concerned that in paragraph 3.20 of the FAD – which sets out how the ICER threshold was decided – the only factor mentioned was uncertainty. The panel did not judge that the committee was obliged to discount uncertainty in the data solely because of the rarity of the condition. However, the panel judged that rarity is a relevant factor to consider when committees weigh the importance of uncertainty in modifying the ICER threshold. The panel were not persuaded by the committee's argument that rarity was less important in this appraisal because of the high quality of the data, as this seemed at odds with their focus on the uncertainty in the data. The panel was also concerned by the implication at the hearing that the committee may have given less detailed consideration to these points because they had not seen any ICERs below £30,000 (particularly given that they had seen ICERs close to this). The panel concluded that the reasoning in the FAD was not

sufficient for the reader to understand how the ICER threshold was reached, in particular how rarity had been weighed in the committee's consideration of uncertainty, but also with regard to how factors other than uncertainty had been weighed in the decision-making.

30. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 1a.2: The appraisal committee's conclusion that "it had not been shown if daratumumab in combination improves overall survival" disregards substantial evidence submitted by Janssen in support of complete haematological response as a surrogate endpoint for overall survival

31. This appeal point was considered alongside Janssen appeal point 2.2 at the hearing, so the following should be read in conjunction with that section of this decision letter. In determining this point 1a.2 the panel had regard to the full discussion at the hearing in relation to this point and point 2.2.

32. Dr Adela Williams, for Janssen, said that the conclusion in section 3.7 of the FAD that "it had not been shown if daratumumab in combination improves overall survival" (OS) appeared to disregard important evidence submitted by Janssen. Firstly, the importance and clinical significance of complete haematological response (CR) to overall survival that had been acknowledged by the Scottish Medicines Consortium as the basis of its recommendation. Secondly, the importance of major organ deterioration progression free survival (MOD-PFS) that was approved as an endpoint by the Food and Drug Administration and the European Medicines Agency. Thirdly, additional data from the ANDROMEDA trial at a median follow-up of 20.3 months showing a modest numerical survival benefit. Whilst some of this evidence was described in the FAD there was no indication that it was taken account of by the committee. Further, she stated the text at the beginning of the FAD appeared to suggest daratumumab in combination does not improve overall survival.

33. Dr Charles Crawley, for NICE, said that the committee accepted the strong correlation between haematological response and OS and accepted that this was a surrogate marker for OS. They did have some concerns about whether confounding factors might influence this relationship. They brought this back

to the second committee meeting, but further analysis did not resolve the issue. The committee therefore concluded that they had not seen evidence proving that daratumumab improves OS, but there was no evidence that it did not do so: this was a case of absence of evidence rather than evidence of absence of effect. A projected survival benefit was incorporated into the economic model used at the first committee meeting. At the second meeting, the company presented data applying an increased survival benefit based on an updated analysis of the ANDROMEDA data. The committee was not happy with this approach, as the company had applied this increased benefit to all response groups (not just those with a complete or very good partial response). In fact, even with this increased projected survival benefit, there were no ICERs within the range normally considered an acceptable use of NHS resources.

34. In response to questions from the panel, Dr Adela Williams said that the question about the relevance of complete haematological response is front and centre of this appraisal. The committee's acceptance that this is a surrogate marker of OS is inconsistent with stating that no OS benefit of daratumumab has been shown. She did not argue that the committee had not been aware of the relevant data, but rather that they did not explain whether or how this linked to their conclusion on whether daratumumab has an OS benefit.

35. Henry Edwards, for NICE, said that the FAD is a short document that attempts to summarise complex issues with a goal of helping patients and clinicians to understand the decision making. He stated that the committee had given careful consideration to this issue, but they would be happy to explain this more clearly in the FAD if needed. He went on to emphasise that the committee has not stated that there is not or may not be an OS benefit from daratumumab, only that it had not seen one.

36. The appeal panel concluded as follows. They accepted that the committee had been aware of the totality of data relevant to whether daratumumab improves OS, and did not accept that they had disregarded this. The panel noted that paragraph 3.7 of the FAD sets out reasoning for the committee's conclusions on overall survival, and accepted that the statement that "it had

not been shown if daratumumab in combination improves overall survival" was intended to mean that this has not been demonstrated definitively with primary data rather than that it was not likely. However, the panel was concerned that this statement appeared inconsistent with the committee's view that complete response is a surrogate marker of OS, and could imply to readers of the FAD that economic modelling had assumed no survival benefit (although this was not the case). The panel were also concerned by the statement in the lay summary of the FAD that "the treatment has not been shown to increase how long people live". The prominence given to this statement in a summary of the document implied that this may have been a key factor in decision making. Overall, the panel concluded that the drafting of the FAD was sufficiently unclear to make it difficult for the reader to understand how a decision had been reached without further information from the committee, and therefore constituted unfairness.

37. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 1a.3: The fact that an expert haematologist was not invited to the first meeting of the committee was not adequately corrected by inviting such an expert to the second meeting because issues such as the significance of complete haematological response were not discussed.

38. This appeal point was considered alongside Myeloma UK appeal point 1a.1 at the hearing, so the following should be read in conjunction with that section of this decision letter. In determining this point 1a.3 the panel had regard to the full discussion at the hearing in relation to this point and Myeloma UK appeal point 1a.1.

39. Dr Margaret Wan, for Janssen, stated that there are only a handful of haematologists in the UK who specialise in this condition, so it was crucial that one of these was present at the committee meetings. Dr Jenny Pinney, consultant nephrologist, highlighted this deficiency during the consultation phase. Without this expertise, the committee would find it more difficult to interpret the treatment goal or the association between CR and overall survival. This was a critical factor in the committee's conclusion that there was uncertainty about the effectiveness of daratumumab. The attempt to address this by inviting Dr Mamta Garg to the second committee meeting

failed because the fundamental importance of haematological response was not revisited. Although Dr Mamta Garg was asked about plausibility of the modelling, there was a superficial discussion and lack of context, and it was not clear that her contribution was fully considered. Dr Margaret Wan suggested that, had there been a discussion of the correlation between CR and OS, this would have demonstrated the effectiveness of daratumumab.

40. Henry Edwards, for NICE, said that input from clinical and patient experts is truly valued by NICE. He pointed out that the committee meeting is not the only opportunity to engage with the appraisal process. He also explained the process for sourcing clinical input. A stakeholder list is drafted at the start of an appraisal process. NICE then asks for nominations of clinical experts from consultees. The chair then selects experts from the nominees, taking into account the NICE policy concerning conflicts of interest. For this appraisal, the committee understood that this is a multi-system disease, with multiple specialties involved in treatment. NICE did receive two nominations of haematologists, but concluded that they were too conflicted to participate in the committee meetings. Dr Charles Crawley pointed out that the decision not to accept the two nominations had been made by his predecessor who had stepped down as committee chair. The committee then sought to mitigate this by selecting three clinical experts rather than two as is usual and by ensuring these experts played a very active role at the first committee meeting. Dr Charles Crawley acknowledged that none of these experts were haematologists. They invited Dr Mamta Garg to the second committee meeting, even though clinical experts are not usually invited at this stage in the process. In addition, a haematologist was involved in the scoping workshop, a haematologist advised the company on their submission and a haematologist gave advice to the Evidence Review Group (ERG). Furthermore, he asserted that the committee did understand the value of CR and its relationship with OS. He explained that the reason this was not revisited was because the committee had already accepted CR as a surrogate marker. While it was unfortunate there was no haematologist at the first meeting as the chair felt those nominated were conflicted, the committee considered the expert input received was adequate.

41. Dr Charles Crawley, for NICE, explained that NICE is dependent on stakeholders for nominating experts and this can be difficult, particularly regarding conflicts. He said the committee discussed three time points and the reason the committee did not return in the second committee meeting to the question of the time point to assess haematological response was that it had already agreed to consider both 3 and 6 months. He acknowledged that he is a consultant haematologist but confirmed that this was not relevant as it was not his role when working for NICE as committee chair.

42. In response to questions from the panel, Henry Edwards confirmed that the committee would have liked to have a treating clinician (i.e. a haematologist) present at the first meeting. He was unsure whether, after the nominated experts had been rejected based on conflicts of interest, NICE had sought alternative suggestions. He confirmed that the three specialists at the first committee meeting had expertise in AL amyloidosis (including one who is a consultant in renal medicine at the National Amyloidosis Centre).

43. In response to questions from the panel, Nicola Trevor, for Janssen, explained the key questions they felt should have been posed to a haematologist that were not asked of Dr Mamta Garg at the second meeting. She said that Dr Mamta Garg was asked about plausibility of the OS curves and clinical extrapolation, but the committee did not revisit the importance of haematological response. Concerning the relationship between haematological response and OS, she agreed the committee had accepted haematological response as a surrogate for OS but said the depth of questioning of Dr Mamta Garg was superficial: the committee should have asked a clinical expert about how important confounding is likely to be and what the importance of response categorisation is. She also explained that Janssen were not informed that their nominations had not been accepted and only became aware that there was no haematologist attending when they arrived at the first committee meeting.

44. Dr Charles Crawley agreed that it would have been desirable to have a haematologist in the first committee meeting but they had decided to proceed when there was not one available given that they had other specialists in AL amyloidosis (albeit not those primarily involved in treatment). He emphasised

that the absence of a haematologist at the first committee meeting had not had an impact on decision making. In particular, the committee recognised the importance of CR as a surrogate marker of OS and understood there was a strong correlation there. They looked in detail at the time point for assessing response. He judged that there were no clinical questions that could have materially affected the committee's conclusions or the recommendation that was reached.

45. The appeal panel concluded as follows. The panel noted the importance of clinical expert advice throughout the technology appraisal process, and agreed that a clinical expert would normally be a treating physician with specific expertise in the condition being considered. The panel judged that it was reasonable for NICE to reject nominated experts based on conflicts of interests, but noted that it may be hard to identify experts without any conflict of interest in a rare disease, so felt it would have been helpful if the basis for this decision had been documented. The panel noted that there was no evidence that NICE had sought an alternative haematologist to participate at the first meeting. The company did not have the opportunity to make an alternative nomination as they were not aware their nominees had been rejected until they arrived at the meeting. The panel commented that NICE may wish to consider amending their procedures to ensure that stakeholders are informed when nominated experts are rejected. The panel noted Dr Charles Crawley's statement that the lack of clinical expert advice at this stage did not affect decision-making but were struck by Professor Ashutosh Wechalekar's description of the clinical expert at the meeting feeling unable to answer the questions posed (see the section of this decision regarding Myeloma UK appeal point 1a.1). The panel agreed that inviting a haematologist to the second meeting could have addressed this deficiency, but in fact Dr Mamta Garg clearly felt that she did not have the opportunity to fully explain her point of view on issues of importance to the appraisal. Overall, the panel therefore concluded that the absence of a treating physician at the first committee meeting amounted to unfairness in this case.

46. The appeal panel therefore upheld the appeal on this point.

Appeal by Myeloma UK

Appeal Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly

Appeal Ground 1a.1: NICE has failed to act fairly by not taking into account the advice and experience of haematologists at every stage of the appraisal process.

47. This appeal point was considered alongside Janssen appeal point 1a.3 at the hearing, so the following should be read in conjunction with that section of this decision letter. In determining this point the panel had regard to the full discussion at the hearing in relation to this point and Janssen appeal point 1a.3.

48. Sarah Love, for Myeloma UK, submitted that what procedural fairness requires depends on the particular circumstances of this appraisal. In particular, management of AL amyloidosis is normally co-ordinated by a haematologist with a special interest in this disease so only a specialist haematologist can give advice on important issues like categorisation of treatment response. She confirmed Myeloma UK agree with Janssen's arguments under Janssen point 1a.3 regarding why a haematologist was required as a matter of procedural fairness from the outset of the appraisal. She quoted parts of NICE's Principles and the methods guide regarding the need for a comprehensive evidence base, emphasising the importance of utilising specialist clinical expertise at all stages of an appraisal.

49. Shelagh McKinlay, for Myeloma UK, explained that she has extensive experience of attending NICE committee meetings, but has never previously encountered a scenario where a treating physician did not participate in every meeting. Although clinical experts were present at the first committee meeting, they were not haematologists with primary responsibility for treating patients with this disease. The presence of a haematologist was vital to validating both the company and ERG cases and critical to ensure that the decision-making was fully informed. Although Dr Mamta Garg attended the second committee meeting, this did not address misconceptions that were by then built into the committee's consideration (specifically concerning how

haematological response should be defined, which dataset to extrapolate OS from and the importance of speed and depth of haematological response).

50. Dr Mamta Garg, for Myeloma UK, confirmed that she attended the second committee meeting. She recalls being shown extrapolated survival curves for different response categories from both ALchemy and EMN23 and asked which better represented clinical practice. She said EMN23, but was not given adequate context or time to elaborate. In particular, she felt that the vital importance of how CR is defined, which renders the ALchemy data inadequate, was not understood by the committee.

51. In response to questions from the panel, Shelagh McKinlay said that Myeloma UK do not normally nominate experts as they expect other consultees to do this. She went on to say that she was concerned about the lack of haematology input at technical engagement as well as at the first committee meeting. She pointed out that the role of a clinical expert at the committee meetings is different from the role of an expert advising the company or ERG, so the fact that there was haematology input into the company case and ERG report did not mitigate the unfairness caused by the absence of a haematologist at the first meeting.

52. Professor Ashutosh Wechalekar, for Myeloma UK, (who did not attend the first committee meeting), stated that a clinical expert who was present at the first committee meeting had communicated with him at the time of the meeting saying that she was being asked questions that she could not answer.

53. Dr Charles Crawley and Henry Edwards, for NICE, responded as set out in paragraphs 40-42 above.

54. The appeal panel concluded, for the reasons set out in paragraph 45, that the absence of an expert haematologist at the first committee meeting did amount to procedural unfairness in this appraisal.

55. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 1a.2: NICE has not acted fairly by failing to allow the National Amyloidosis Centre to nominate its own clinical expert for committee meetings

56. Sarah Love, for Myeloma UK, referred to her points set out in paragraph 48 about the importance of utilising specialist clinical expertise at all stages of an appraisal. She argued that the decision not to include the National Amyloidosis Centre (NAC) as a commentator is a stark and surprising example of difficulties in the process of this appraisal.

57. Professor Ashutosh Wechalekar, for Myeloma UK, explained that the NAC is a national referral centre, funded by the Department of Health and Social Care, which sees the majority of patients with this condition nationally. They undertake an assessment and then patients can go back to their local centre for treatment. They have been involved in all new treatments for the condition and have detailed retrospective databases. A key role of the haematologist in the multidisciplinary team is in the assessment of treatment response. This is particularly important because the evaluation of treatment response has changed over time, and it was a challenge to put this into context for the committee. He said that the ERG also struggled with this and he was last contacted by the ERG about it ten minutes before the second committee meeting. Having an expert nominated by the NAC at the first committee meeting would have helped everyone to understand how response evaluation matters.

58. Henry Edwards explained that NICE engages with hundreds of patients and clinical organisations in 150-200 appraisal scopes every year. In this case, in drafting the scope / stakeholder list, the NAC were omitted. This was an omission rather than a deliberate act. Stakeholder lists typically include 50-70 organisations so organisations can be and are missed mistakenly. Many stakeholders do not contribute, so despite reference in the appraisal to NAC guidance, NICE did not realise the NAC had been omitted. The consultation on the scope provides an opportunity for such an omission to be pointed out to NICE. It specifically asks consultees to let NICE know if they have missed any organisations from the stakeholder list. If anyone had alerted NICE to the absence of the NAC from this list, they would certainly have been added. NICE are not experts on the conditions, so they rely on stakeholders to alert

them to any errors. He emphasised that NICE did not intend to prevent the NAC from participating or nominating its own clinical expert for committee meetings.

59. Shelagh McKinlay, for Myeloma UK, acknowledged that they did not highlight to NICE that the NAC had not been included in the list of stakeholders.

60. Professor Ashutosh Wechalekar stated that he asked the ERG whether he or another NAC haematologist could attend the first committee meeting but was told this was not possible owing to NICE's conflict of interest procedure. He accepted this request was made to the ERG, not to NICE.

61. The appeal panel concluded as follows. The committee agreed during the hearing that not including the NAC as a stakeholder was an omission. The panel acknowledged the challenge that the NICE scoping team face in identifying all relevant stakeholders, and noted that the opportunity for consultees to point out any omissions from this list at consultation is a useful part of the process. It was unfortunate that none of the consultees alerted NICE to the omission of the NAC on this occasion. However, AL amyloidosis is a rare disease where almost every patient is assessed in a single centre. It was therefore of particular importance to include this organisation, the NAC, as a stakeholder. Whilst a clinician from the NAC was present at the first committee meeting, this was not a haematologist. As discussed under Janssen appeal point 1a.3 and Myeloma UK appeal point 1a.1, the panel judged that that the absence of specialist haematology advice throughout the process was unfair. If the NAC had been appropriately included as a stakeholder, they would have had the opportunity to nominate an expert haematologist. The panel therefore concluded that the omission of the NAC as a stakeholder was unfair.

62. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 1a.4: NICE has not acted fairly when applying criteria for determining an acceptable ICER value under the Methods Guide 2013

63. At the hearing, this point was taken together with Janssen's appeal point 1a.1, so this section should be read in conjunction with that section of the decision

letter. In determining this point the panel had regard to the full discussion at the hearing in relation to this point and Janssen appeal point 1a.1.

64. Shelagh McKinlay, for Myeloma UK, stated that paragraph 3.20 of the FAD where the ICER threshold is discussed, fails to discuss all the factors that should have been taken into account in addition to uncertainty. Instead there is a long list of bullet points about the sources of uncertainty. She referred to section 6 of the Methods Guide which says that cost-effectiveness is not the sole basis for decision-making, and subsection 6.2 which notes that the evidence for rare diseases is necessarily weaker. She referred to section 6.3.1 of the methods guide which states the committee does not use a precise maximum acceptable ICER and that consideration of the cost effectiveness of a technology is a necessary, but is not the sole, basis for decision-making. She then referred to section 6.3.3 which sets out factors to be considered in deciding whether a most plausible ICER above £20,000 per QALY gained is an effective use of NHS resources and said that the committee failed to take account of these. She said that setting a low ICER threshold is out of keeping with the approach to rarity in the HST programme and that the committee could have chosen to apply flexibility but did not.

65. Henry Edwards and Dr Charles Crawley, for NICE, responded as set out in paragraphs 18-20 above. Submissions were also made for Janssen, as set out above.

66. Sarah Love, for Myeloma UK, stated that there was a significant transparency issue. It was not enough for the committee to list factors it was aware of and assert these featured in the ICER threshold conclusion. Instead, it should explain how these factored into decision making. It was also not enough for the committee to consider factors in the meeting but not refer to those factors in the FAD or explain how those factors influenced their conclusion.

67. In response to questions from the panel about the clinical need in this condition, Professor Ashutosh Wechalekar, for Myeloma UK, explained that patients with AL amyloidosis are often diagnosed late and this adversely affects their median survival. He described the clinical need as desperate.

68. Shelagh McKinlay pointed out that the ACD stated that the committee had seen ICERs between £34,000 and £62,000. She argued that £34,000 is not a million miles away from £30,000 so it is not the case that the ICERs were nowhere close to being acceptable. Regarding unmet need, she stated that not only is AL Amyloidosis a severe condition but that there is no treatment.

69. Sarah Love said that while £20,000-£30,000 is the usual range of acceptable ICERs, there is no absolute threshold and there should always be an assessment in the round for that particular appraisal. She also referred to 6.3.5 of the Methods Guide ("Above a most plausible ICER of £30,000 per QALY gained, the committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources, with regard to the factors listed in section 6.3.3") and the fact that in the HST process, ICERs of >£100,000 can be acceptable. She quoted the HST guidance which states "a simple utilitarian approach…is unlikely to produce guidance which would recognise the particular circumstances of these very rare conditions" and addresses the vulnerability of small patient groups as well as the extent of evidence and challenges for a company in making a reasonable return. She argued that the vulnerability of a small patient group was applicable to AL amyloidosis even if the other factors may be less so in this case. She suggested it would be very unfortunate if daratumumab "falls between two stools" given the high need / vulnerability of the patient group.

70. Henry Edwards, responded as set out in paragraphs 19, 23 and 26 above.

71. The appeal panel concluded as set out in paragraph 29 above that the reasoning in the FAD was not sufficient for the reader to understand how the ICER threshold was reached, in particular with regard to how rarity had been weighed in the committee's consideration of uncertainty, but also with regard to how factors other than uncertainty had been weighed in the decision-making. The appeal panel therefore upheld the appeal on this point.

Appeal by Janssen

Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.

72. There was no appeal under this ground.

Appeal by Myeloma UK

Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.

73. There was no appeal under this ground.

Appeal by Janssen

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Appeal Ground 2.1: The appraisal committee's conclusions that "both ALchemy and EMN23-UK may be representative of UK clinical practice" are unreasonable.

74. At the hearing, this point was taken together with Myeloma UK appeal point 2.1, so this section should be read in conjunction with that section of the decision letter. In determining this point the panel had regard to the full discussion at the hearing in relation to this point and Myeloma UK point 2.1.

75. Nicola Trevor, for Janssen, explained that in this appraisal, real world evidence was used to model the response in the standard of care arm, and the impact of haematological response on OS. The reason for this is that ANDROMEDA necessarily excluded patients with more severe disease, so did not capture the full licensed population. At the first committee meeting, the committee considered two sources of data (ALchemy and EMN23). It became clear that neither were appropriate because of confounding by treatment switching, and because both used an older approach to categorising haematological response than the ANDROMEDA trial. The committee therefore asked Janssen to adjust the analysis to bring the approach to categorisation of response in line with ANDROMEDA. Janssen could not do this for the ALchemy dataset as they did not have access to patient level data. However, they were able to do this for the UK patients in the EMN23 dataset (EMN22-UK). She pointed out that there is 95% overlap between the patients in ALchemy and EMN23-UK.

76. Dr Charles Crawley, for NICE, explained how the committee approached reaching its conclusions. They were presented at the first committee meeting with two sets of real world data to extrapolate survival beyond the data from ANDROMEDA: ALchemy and EMN-23. They first asked themselves which was most representative of UK clinical practice and then asked which should be used in the economic model. At the first committee meeting they were presented with the original EMN-23 cohort, of which only 38% were UK patients and many of which did not receive bortezomib based treatment regimens. They therefore concluded that ALchemy was more representative of UK practice. They did note the difference in response categorisation between ANDROMEDA and ALchemy and asked for this to be addressed. At the second meeting they had access to the ALchemy data, and the EMN23-UK data which contained exclusively UK patients and had been re-classified to use the current criteria for haematological response. The committee concluded that both are representative of UK practice, particularly as they include virtually the same patients. They then went on to ask themselves which data should be used in the modelling. EMN23-UK was preferred in the modelling because the committee recognised the importance of the re-classification of the data. However, they did have some concerns about the 18-22% missing data in this sample, and asked themselves whether the data were missing at random. The committee asked for further data on how this might impact the validity of the data but were not able to obtain it. They therefore used ALchemy as a scenario analysis or “sense check”, but EMN-23 was the primary basis for the economic model. He added that none of the ICERs the committee saw were in the range normally considered an acceptable use of NHS resources. He reiterated the committee considered this issue in two stages: first, what was representative of UK clinical practice; second, what should be used in the modelling? They felt they could not say ALchemy did not reflect UK clinical practice.

77. Henry Edwards, for NICE, emphasised that the committee did not state a preference for ALchemy in the FAD, and that using the term “may” be representative of UK practice reflected uncertainty about both data sources. He found it challenging to understand how this statement could be considered

unreasonable when the two cohorts are made up of essentially the same patients.

78. In response to questions from the panel about where the committee's preference for EMN23-UK in the economic model appears in the papers, Nicola Trevor said that the papers suggest that ALchemy and EMN23-UK were given equal weight.

79. The appeal panel concluded as follows. The panel were aware of the importance of how CR is defined, as explained by Professor Ashutosh Wechalekar. They agreed that the patients in both the ALchemy and EMN23-UK cohorts were representative of UK practice (and indeed they were essentially the same patients) but noted that the criteria for assessing haematological response in ALchemy are not representative of current UK practice. The approach Dr Charles Crawley described at the hearing (preferring EMN23-UK for economic modelling, but using ALchemy as a "sense check" given uncertainty arising from missing data in EMN23-UK) seemed reasonable to the panel. However, the panel could find no documentation in the papers to show that EMN23-UK was preferred for modelling, nor were the committee able to point out such a reference during the hearing. In a section of the FAD concerning modelling, at paragraph 3.11, the committee conclude that "the choice of dataset, that is, EMN23-UK or ALchemy is uncertain". In the slides from the second committee meeting there is no indication that the ICERs on slide 37 using EMN23-UK were preferred. If anything, the title of slide 38 (which includes "committee preferred assumptions") seems to imply that these ICERs using ALchemy were preferred. Overall, the panel judged that the FAD gave the impression that the committee weighted EMN23-UK and ALchemy approximately equally. This seemed strikingly at odds with the clear reasons for preferring EMN23-UK given by the committee themselves at the hearing, as well as Professor Ashutosh Wechalekar's opinion that ALchemy should not be given any weight (see paragraph 94). The panel therefore concluded that the conclusion that both ALchemy and EMN23-UK may be representative of UK clinical practice did not adequately capture how the committee handled these two datasets and was so unclear as to be unreasonable.

80. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 2.2: The committee's conclusion that "it had not been shown if daratumumab in combination improves overall survival" conflicts with the balance of available evidence.

81. This appeal point was considered alongside Janssen appeal point 1a.2 at the hearing, so the following should be read in conjunction with that section of this decision letter. In determining this point the panel had regard to the full discussion at the hearing in relation to this point and point 1a.2.

82. Andrew Ternouth, for Janssen, described the (OS) data from ANDROMEDA. Median OS was not reached in either arm but at 18 months and 20 months survival was higher in the daratumumab group. Commonly, mature OS data are not available at the time of an appraisal, so a submission is made using a surrogate endpoint. NICE uses three levels of data: Level 3 (biological), Level 2 (non-interventional studies) and Level 1 (Randomised Controlled Trials (RCTs)). Janssen presented a substantial amount of Level 3 and 2 data to support the relationship between timing and depth of haematological response and OS. He argued that this position is consistent with guidelines that recommend CR as a treatment target and with expert testimony during the appeal hearing. He concluded that the totality and consistency of evidence supports an OS benefit from daratumumab.

83. During discussion of Myeloma UK appeal point 2.1, Professor Ashutosh Wechalekar, for Myeloma UK, explained that one reason no survival benefit has yet been seen in ANDROMEDA is because patients with more advanced disease could not be included in the trial. He said there are three clear facts: that CR (as currently defined) translates into OS, that this applies at all stages of disease, and that the rate of CR with daratumumab in combination is much higher than with standard of care.

84. Dr Charles Crawley, for NICE, responded as set out in paragraph 33 above.

85. In response to questions from the panel, Dr Charles Crawley, said that the committee accepted that complete response was a well-established surrogate marker of OS. They also noted the association between MOD-PFS and OS.

However, they did have concerns about potential confounders that were not addressed by additional analysis. In terms of implementation in the model, the committee did take OS into account. He referred to slide 16 from the second committee meeting where all the modelled survival curves show a survival benefit and explained that this informed the model and calculations of cost-effectiveness. They also considered the additional survival benefit modelled by Janssen as a scenario. As neither of these produced an acceptable ICER, they did not have to make a final conclusion on this point. However, the committee did conclude that they could not say that primary data had demonstrated a survival benefit.

86. Yelan Guo, for NICE, said that whilst the committee recognised in the FAD that complete response is a surrogate marker the question was how strong this association is. She said that the ratio of 1.066 for OS reported in the 12 month landmark analysis of the ANDROMEDA trial was a post-hoc analysis without confidence intervals. Therefore, from a technical perspective, there is uncertainty about whether daratumumab has an OS benefit based on current data.

87. Henry Edwards, for NICE, said that the committee has not stated that there is not or may not be an OS benefit from daratumumab, only that it had not seen one.

88. The appeal panel concluded as follows. During the hearing there seemed to be a consensus on two points, with which the panel also agreed. On the one hand, the data from ANDROMEDA are not mature, so it is not possible to say unambiguously that daratumumab improves overall survival. On the other hand, CR and MOD-PFS are valid and appropriate surrogate markers of overall survival. The panel accepted that the committee intended their statement to mean that an OS benefit had not been definitively shown with primary data. However, the panel also accepted that the statement could be read to mean that the balance of evidence was not in favour of an overall survival benefit from daratumumab. Whilst the slides from the second committee meeting made clear that an overall survival benefit had been incorporated into economic modelling, this was not clear in the FAD. The panel also noted that the statement that “the treatment has not been shown to

increase how long people live" is in the lay summary, implying it may have been a key factor in decision-making. The panel found it particularly hard to reconcile the committee's conclusion that daratumumab has no overall survival benefit with the committee's acknowledgement that CR was a close surrogate of survival and that the drug clearly benefited MOD-PFS, given that the committee accepted that organ failure was the commonest cause of death. Overall, the panel felt that the strength of the evidence taken together made it unreasonable to conclude it had not been shown if daratumumab in combination improves overall survival, as this was likely to be read by the intended audience as suggesting that daratumumab does not have an OS benefit, even if this is not the meaning the committee intended.

89. The appeal panel therefore upheld the appeal on this point.

Appeal by Myeloma UK

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Appeal Ground 2.1: The appraisal committee's conclusion that "both Alchemy and EMN23-UK may be representative of UK practice" is unreasonable in light of the evidence submitted.

90. At the hearing, this point was taken together with Janssen appeal point 2.1, so this section should be read in conjunction with that section of the decision letter. In determining this point the panel had regard to the full discussion at the hearing in relation to this point and Janssen point 2.1.

91. Sarah Love, for Myeloma UK, said that it is important not to overstate what it means in law to say that a decision is unreasonable, and referred to relevant judgements. In particular, where a technical error is made, the error does not have to "jump off the page" or be readily explained to a lay person to be unreasonable, but it should be incontrovertible once explained. She argued that the conclusion that both ALchemy and EMN23-UK may be representative of UK practice was central to the decision not to recommend daratumumab, because it informed the committee's conclusion about OS.

92. Professor Ashutosh Wechalekar, for Myeloma UK, explained that ALchemy is a UK observational study of over 1600 patients since 2007. EMN23 is a

cohort bringing together data from a number of European centres including the UK. The UK patients in both datasets are the same. He explained that the International Society of Amyloidosis have used different criteria for the definition of haematological response over time (2005, 2012 and 2020). The data in the published ALchemy cohort uses the 2012 criteria. The criteria were updated in 2020 because clinicians had noted that some patients were getting a deep haematological response to novel therapies, and had excellent outcomes, even though did not quite meet the 2012 criteria for "complete response". Once the criteria were updated, it became clearer that depth of haematological response was a strong predictor of outcome. For instance, in the original analysis of EMN23 data (using the 2012 criteria) there appeared to be little difference in survival between patients with CR and very good partial response (VGPR). Once the 2020 criteria were used, there was a dramatic difference in survival between these two groups. After the first committee meeting, Janssen asked Professor Ashutosh Wechalekar's team for re-categorised EMN-23 data using the 2020 criteria. This necessarily resulted in some missing data, but the dataset still included over 900 patients.

93. Dr Charles Crawley and Henry Edwards, for NICE, responded as set out in paragraphs 76and 77 above.

94. Professor Ashutosh Wechalekar, stated that despite the missing data, the re-analysis of EMN23-UK was very rigorous and included a large number of patients. He said that it would be unreasonable to attach any weight to the ALchemy data.

95. The appeal panel concluded as set out in paragraph 79 that the committee's conclusion that both Alchemy and EMN23-UK may be representative of UK clinical practice was unreasonable.

96. The appeal panel therefore upheld the appeal on this point.

Conclusion and effect of the appeal panel's decision

97. The appeal panel therefore upholds the appeal on the following grounds: Janssen 1a.1, 1a.2, 1a3, 2.1, 2.2 and Myeloma UK 1a.1, 1a.2, 1a.4 and 2.1.

98. The appraisal is remitted to the appraisal committee who must now take all reasonable steps to correct the issues identified above. Specifically:

99. **Janssen 1a.1 and Myeloma UK 1a.4:** the committee should reconsider the significance and relevance of rarity and other factors listed in the methods guide to ensure they have been properly taken into account in determining the ICER threshold for this appraisal. Should this result in a change to the threshold, the committee will need to assess the impact of this (if any) on the overall recommendation. In any event the decision-making around the ICER threshold should be adequately explained in the FAD.

100. **Janssen 1a.2, Janssen 1a.3, Myeloma UK 1a.1, Myeloma UK 1a.2 and Janssen 2.2:** the committee should re-evaluate the data on surrogate markers of OS and reconsider to what extent they might inform a judgement on OS. To assist in this they should take steps to obtain further advice from a specialist haematologist, or from specialists at the National Amyloidosis Centre. In the light of this they should reconsider the balance of evidence on the effect of daratumumab on overall survival and ensure that their review of these data is clearly explained in the FAD.

101. **Janssen 2.1 and Myeloma 2.1:** the committee should reconsider whether both ALchemy and EMN23-UK may be representative of UK practice, and clarify in the FAD how they used these data for the purpose of economic modelling.

102. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis (ID3748)

Submission addendum

October 2023

File name	Version	Contains confidential information?	Date
ID3748 Daratumumab combination for newly diagnosed AL amyloidosis Submission Addendum	V1	Yes	13/10/2023

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Janssen submission addendum – October 2023

Contents

Executive summary

- Janssen welcomes the opportunity to provide an addendum to our submission for daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (DBCd) for untreated systemic amyloid light-chain amyloidosis (AL amyloidosis).
- Following publication of the appeal decision and confirmation that the appeal panel had upheld the five [5] appeal points raised by Janssen and the four [4] points raised by Myeloma UK, Janssen has prepared this submission addendum for consideration by the Committee ahead of the third appraisal committee meeting (ACM) scheduled in November 2023.
- Furthermore, as requested by NICE, Janssen has endeavoured to provide additional evidence and analyses (discussed further on Page 8 with results presented in the Appendix on Page 12) regarding:
    - The relationship between haematological response, major organ deterioration and overall survival, and
    - The EMN23-UK dataset and potential bias introduced by missing data
- With the considerations resulting from the appeal, alongside an updated patient access scheme (PAS) discount, revised cost-effectiveness results for DBCd fall within a reasonable NICE willingness-to-pay threshold, representing a cost-effective use of NHS resources. DBCd is accordingly suitable for routine commissioning. However, should the NICE Committee consider that further evidence collection for DBCd is required, we maintain that patient access via the Cancer Drugs Fund (CDF) could be a valid alternative route.
- We remain committed to working with all relevant stakeholders, including NICE and NHS England, to secure access for patients with newly diagnosed AL amyloidosis to DBCd, the first licensed treatment for this rare, life-threatening condition.

Summary of key appeal panel outcomes and their impact

For ease of reference, the key conclusions of the appeal hearing have been summarised below, along with Janssen's response to these conclusions.

Janssen 1a.2, Janssen 1a.3, Myeloma UK 1a.1, Myeloma UK 1a.2 and Janssen 2.2:

- "*The appeal panel concluded that the committee should re-evaluate the data on surrogate markers of overall survival (OS), and reconsider to what extent they might inform a judgement on OS. To assist in this they should take steps to obtain further advice from a specialist haematologist, or from specialists at the National Amyloidosis Centre. In the light of this they should reconsider the balance of evidence on the effect of daratumumab on overall survival and ensure that their review of these data is clearly explained in the FAD*."
- As referred to in Janssen's original company submission (Section B.3.3.3) and further detailed on page 5 in this document, there is a substantial body of evidence supporting the prognostic relationship between depth of haematological response and improved overall survival in patients with newly diagnosed AL amyloidosis.[1-8] This is consistent with the views of clinical experts expressed during previous committee meetings for this appraisal, and is discussed further in the additional evidence and analyses section (presented on Page 8).
- The association between haematologic response and OS in turn underlies the primary treatment goal of front-line treatment, which is for the patient to achieve the best possible haematologic response.[9] Organ recovery is strongly associated with the depth of haematological response achieved.[10-13] The deeper the haematological response, the more likely organ response will occur (higher organ response rates) and the longer the survival.[8]

Accordingly, the expectation that the statistically and clinically significant improvements in haematological response demonstrated by DBCd over BCd in the ANDROMEDA trial,[14] and the resultant improved organ response rates, will translate into survival benefits for patients is strongly evidence-based.

- The relationship between haematologic response and survival is captured in Janssen's revised approach to modelling the OS benefit associated with daratumumab maintenance therapy. As described further below, results from ANDROMEDA demonstrate that haematological response deepens, and is sustained for longer, following receipt of daratumumab maintenance after Cycle 6.[3, 15-18] This is expected to confer a survival benefit over-and-above the superior responses achieved with DBCd by Cycle 6. Importantly, the revised approach to modelling a survival benefit for daratumumab maintenance therapy addresses the NICE Committee's previous concerns around the application of this benefit independent of haematological response.

Janssen 2.1 and Myeloma 2.1:

- "*The committee should reconsider whether both ALchemy and EMN23-UK may be representative of UK practice, and clarify in the FAD how they used these data for the purpose of economic modelling*."
- As described in the summary document of the appeal hearing,[19] following the first committee meeting, the EMN23-UK data were re-classified using current criteria used in the UK to assess haematologic response. It was not possible to conduct this re-analysis for ALchemy, since Janssen do not have access to these data.
- Underscoring the strength and relevance of these data, Professor Wechalekar clarified at the appeal hearing that "*despite the missing data, re-analysis of the EMN23-UK was very rigorous and included a large number of patients*."[19] He further noted it would be "*unreasonable to attach any weight to the ALchemy data*".
- Accordingly, Janssen consider the re-classified EMN23-UK data to be the only data source suitable for representing outcomes with standard of care in the UK. For this reason, the re-classified EMN23-UK dataset has been maintained as the source of long-term OS extrapolations in the updated base case analysis, as detailed below.

Janssen 1a.1 and Myeloma UK 1a.4:

- "*The committee should reconsider the significance and relevance of rarity and other factors listed in the methods guide to ensure they have been properly taken into account in determining the ICER threshold for this appraisal*."
- Newly diagnosed AL amyloidosis patients currently have no approved treatment options available with access to novel myeloma approved therapy restricted by strict Blueteq criteria. The substantial unmet need for a licensed treatment option for these patients was captured during the appeal by the patient expert, who described the significant impact the condition has on his life.[19] This unmet need, as well as the improvement in quality of life and other benefits DBCd is expected to bring to patients that cannot be captured in economic analysis, was described in detail in Janssen's response to the Appraisal Consultation Document.
- It is of the utmost importance that the rare nature of AL amyloidosis, current lack of effective licensed treatments, and significant burden experienced by patients as a result of this disease are considered in the Committee's determination of the ICER threshold for this appraisal.

Summary of relevant updates to cost-effectiveness and the economic model

Daratumumab patient access scheme

- Cost-effectiveness for DBCd has improved since publication of the original negative FAD with a change in the daratumumab PAS discount from [redacted] submitted as part of the Appraisal Consultation Document (ACD) response to [redacted], offering further value for money to the NHS.
- The cost-effectiveness results presented in this submission addendum have been updated to reflect the new PAS discount for daratumumab, with all other drug costs in the analysis (combination and subsequent treatments) presented at list price.

Inclusion of a survival benefit of daratumumab maintenance treatment

- As described in Section B.3.2.2 of the original Company submission, survival extrapolations in the cost-effectiveness model are based on the depth of haematological response at Cycle 3 or Cycle 6. Data from ANDROMEDA, however, clearly demonstrate that response outcomes continue to deepen beyond Cycle 6 of treatment and that these responses are more durable in patients receiving DBCd than BCd. These data, which have been previously presented in Table 1 of Janssen's response to Technical Engagement and Table 14 of Janssen's ACD response, are summarised in Table 1 below, and presented in full in Table 4 and Table 5 of the Appendix.

Table 1: Summary of rates of CHR and VGPR (ANDROMEDA ITT analysis set, 14th February 2020 data cut-off, 13th November 2020 data cut-off) and CHR maintenance at Month 24

Response	BCd (N=193)	DBCd (N=195)
CHR, % (95% CI)	**IA1:** 18.1 (13.0, 24.3) **12-month landmark:** 19.2 [redacted]	**IA1:** 53.5 (46.1, 60.5) **12-month landmark:** 59.0 [redacted]
VGPR, % (95% CI)	**IA1:** 31.1 [redacted] **12-month landmark:** [redacted]	**IA1:** 25.1 [redacted] **12-month landmark:** [redacted]
CHR maintenance to Month 24, n/N (%)	**Month 3 CHR:** [redacted] **Month 6 CHR:** [redacted]	**Month 3 CHR:** [redacted] **Month 6 CHR:** [redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ITT: intention-to-treat; VGPR: very good partial response.

- As discussed above, the achievement of a deeper and more sustained haematologic response following daratumumab maintenance is expected to translate into a survival benefit as this relationship between depth of response and OS outcomes is well established. This is further supported by results from a US observational study which analysed 107 patients with AL amyloidosis treated with daratumumab monotherapy between 2017 and 2020.[20] This study showed that patients who received daratumumab monotherapy for more than 12 cycles experienced significantly longer major organ deterioration progression-free survival (MOD-PFS) and OS than those who received it for ≤ 12 cycles, with a multi-variate analysis identifying achievement of at least a VGPR as being independently associated with these long-term outcomes. While factors such as small patient numbers, receipt of daratumumab monotherapy for the entire treatment course (rather than in combination with BCd for the first six cycles) and the prior treatment history of these patients should be taken into account when considering generalisability of this study, these data nevertheless support the clinical

plausibility of daratumumab maintenance therapy beyond Cycle 6 conveying a long-term survival benefit to patients.[20]

- As such, Janssen consider the Committee's conclusion not to apply a survival benefit of daratumumab maintenance treatment to represent an important unquantified benefit of daratumumab treatment, since the associated costs of maintenance treatment from Cycle 7 to 24 are included in the economic model but the long-term survival benefit expected to accrue from deeper and more durable responses is not. The conservative nature of the model in this sense was also highlighted by the ERG during the first committee meeting for this appraisal.
- Janssen note the Committee's conclusion in the FAD that modelling an expected survival benefit for daratumumab maintenance treatment may be *'reasonable in principle'* however *'applying this benefit independent of haematological response categories was unlikely to be appropriate'*. In response, Janssen has taken an alternate approach to implementing the survival benefit associated with daratumumab maintenance therapy beyond Cycle 6 in the economic model, and this has been applied in the company revised base case. Specifically, the 4.4% efficacy uplift calculated based on the 12-month landmark analysis has been applied to the CHR and very good partial response (VGPR) categories **only**, rather than all response categories. This revised approach takes into consideration the Committee concerns per the FAD and the helpful clarification comments provided by the Committee Chair at the NICE appeal hearing.

Administration costs

- Administration costs for bortezomib and daratumumab have been updated in line with the Committee preferred assumptions presented in the FAD: a cost of £1,127 per cycle has been applied to both the DBCd and BCd arms for Cycles 1 to 6, and a cost of £161 per cycle has been applied for daratumumab maintenance monotherapy from Cycle 7 onwards.

Revised economic base case and scenario analysis results

- Considering the Committee preferred assumptions documented in the FAD, alongside further clarification published in the NICE Appeal Decision, Janssen present an updated economic base case in which the following changes have been implemented as compared with the economic model submitted at the ACD response stage:
    - Updated PAS discount for daratumumab
    - Daratumumab maintenance multiplier applied to CHR and VGPR haematological response categories only
    - Updated administration costs for bortezomib and daratumumab
- In line with the extrapolations implemented in the base case submitted in the ACD response document, the extrapolations for the base case analysis were as follows: CHR: log-normal; VGPR: log-logistic; PR: log-normal; NR: log-normal.
- Revised base case results are presented in Table 2, and demonstrate that DBCd represents a cost-effective use of NHS resources at a willingness-to-pay threshold of £30,000 per QALY, which Janssen consider to be a reasonable threshold given the rare nature and substantial unmet need associated with this condition.
- In addition, we present the following scenario analyses to further illustrate the cost-effectiveness of DBCd:
    1. No additional survival benefit with daratumumab monotherapy

        - This scenario analysis has been conducted to replicate the analysis performed by the EAG in their critique of Company comments on the ACD.
    2. Six-month decision-tree exit timepoint
        - Consistent with Committee conclusions per the FAD which recognised "*the 6-month timepoint may represent a better proxy for overall survival*", Janssen consider this a more suitable timepoint to inform long-term survival estimates (the key area of decision uncertainty) than a three-month decision-tree exit timepoint.
    3. Combined scenario (no additional survival benefit with DBCd *and* six-month decision tree exit timepoint)
    4. Health state utility values (HSUVs) as per UK clinician estimations at an advisory board
        - As discussed in Janssen's response to Technical Engagement, UK clinical experts consulted confirmed that the health-related quality of life (HRQoL) benefits of treatment in AL amyloidosis are likely to be established only after approximately one year following initiation of frontline treatment. Furthermore, in a recent publication based on HRQoL data collected from the ALchemy study, an improved change from baseline in SF-36v2 scores at Month 12 was observed.[21] These data clearly establish the validity of clinical expert expectation for HRQoL improvement one year post initiation of frontline treatment. While the ALchemy study represent a less suitable source for efficacy outcome as compared with the EMN23 study, these HRQoL data specifically are valuable in their validation of HRQoL benefits being established over a longer period of time than is available from the ANDROMEDA study (and since the EMN23 study did not collect such data at any timepoint). As such, a scenario analysis in which utility values sourced from clinician estimates (presented in Section B.3.4.1 of the original Company Submission) is presented.

- Results from these scenario analyses are presented in Table 3.
    - In scenario analysis 1, there is a marginal increase in the ICER, however, as described above, Janssen consider this scenario overly conservative as it disregards a wealth of clinical evidence that supports improved long-term survival outcomes driven by deeper haematological responses.
    - The results of scenario 2, whereby haematological response is assessed at 6-months, illustrates a lower ICER compared to the base case, comfortably below a £30,000 per QALY willingness-to-pay threshold.
    - Scenario analysis 3, which combines 1 and 2, also provides an ICER of less than £30,000 per QALY.
    - The results of scenario 4, in which HSUVs are informed by an advisory board with UK clinicians, illustrates a lower ICER compared to the base case, comfortably below a £20,000 per QALY willingness-to-pay threshold.

Table 2: Revised base case results (daratumumab PAS price; all other drug costs at list price)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
BCd	74,087	4.21	6.49	-	-	-	-
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,321

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 3: Scenario analysis results (daratumumab PAS price; all other drug costs at list price)

#	Treatment	Total			Incremental			ICER (£/QALY)
		Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
Base case	BCd	74,087	4.21	6.49	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,321
1	BCd	74,087	4.21	6.49	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,537
2	BCd	68,904	4.15	6.24	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,398
3	BCd	68,904	4.15	6.24	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24,442
4	BCd	74,087	3.70	6.49	-	-	-	-
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,510

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALYs: quality-adjusted life years.

Analyses requested by NICE

- Ahead of the third committee meeting, NICE have requested additional evidence and analyses relating to the following two topics:
    1. Relationship between haematological response, major organ deterioration and overall survival
    2. EMN23-UK dataset and potential bias introduced by missing data

Relationship between haematological response, major organ deterioration and overall survival

- As described in the 'Summary of key appeal outcomes and their impact' section, a wealth of evidence is available that supports the relationship between haematologic response and overall survival, and that improvements in organ response represent an intermediary step between these two outcomes.
- This relationship is further supported by a recent meta-analysis assessing the prognostic utility of haematologic response for overall survival in patients with newly diagnosed AL amyloidosis published by Kastritis et al.[22] Nine observational studies (incl. ALchemy) reporting haematologic complete response (CR) or very good partial response (VGPR) and OS hazard ratios identified in a systematic literature review (SLR) were incorporated into a meta-analysis.[22, 23] Note that the EMN23 study was excluded due to the potential overlap with patient populations of other studies included in the meta-analysis (e.g. ALchemy). Full details of the SLR have been published by Lee *et al.*, 2022.[23]
- In the meta-analysis, a strong relationship between achievement of CR or VGPR and improved OS was observed (HR 0.21 [95% CI 0.13–0.34] and HR 0.21 [95% CI 0.17–0.26] respectively). In particular, patients achieving CR showed better OS than those achieving VGPR, suggesting

achieving CR has prognostic value. Despite the small number of eligible studies (consistent with the rarity of the disease) and differences across the studies included in the meta-analysis, the authors concluded that the consistency of results provides evidence that early haematologic response is a strong patient-level surrogate for long-term OS in patients with AL amyloidosis receiving frontline therapy.[22] This conclusion meets Level 2 of evidence for surrogate relationships as defined in Section 4.6.6 of the NICE Process and Methods Manual (PMG36, 2022), where consistent association between surrogate endpoint and final outcomes is derived from observational studies in addition to the biological plausibility of the relationship.[24]

- In response to the original ACD, Janssen explored the risk of confounding in the relationship between haematological response and overall survival by performing a multivariate analysis of patient baseline characteristics from ANDROMEDA who achieved CHR at 3- and 6-months (Janssen ACD response, Appendix 4). Janssen affirm that the analysis conducted was methodologically robust, yet consequent of the relatively small sample and few OS events, the model did not converge leading to uninformative results.
- Janssen has been unable to update the multivariate analysis as requested by NICE as the interim analysis (11.4 months median follow-up) from ANDROMEDA remains the most recent datacut available reporting OS. It is important to be mindful that the low event rate from ANDROMEDA is a positive outcome for patients since it means many patients with CHR at 3- and at 6-months remain alive. Indeed, consequent of the low event rates in ANDROMEDA, [redacted].

EMN23-UK dataset and potential bias introduced by missing data

- As requested by NICE, the following are presented in the Appendix below:
    a) Kaplan-Meier (KM) curves of overall survival at three and six months based on the original EMN23 dataset, the unadjusted EMN23-UK dataset (i.e., before re-categorisation to align with response criteria in ANDROMEDA), compared to the ALchemy dataset. In the absence of individual patient data (IPD), the KM data from each source were first digitised using software and the Guyot algorithm then used to produce pseudo-IPD to compare outcomes on the same plot (Note: IPD were used by the EMN group to produce KM curves for the EMN23-UK data, which were shared with Janssen. Due to time constraints, the EMN group were not able to anonymise IPD in time to share with Janssen for the purpose of this addendum).
        - KM curves for overall survival at three months based on the original EMN23, unadjusted EMN23-UK and ALchemy datasets are presented in Figure 1–Figure 4 for patients achieving CR, VGPR, PR and NR, respectively.
        - KM curves for overall survival at six months based on the original EMN23, unadjusted EMN23-UK and ALchemy datasets are presented in Figure 5–Figure 8 for patients achieving CR, VGPR, PR and NR, respectively.
        - The analysis at three months show some differences with separation in the unadjusted EMN23-UK and ALchemy curves. The ALchemy survival is higher relative to EMN23-UK for CR but lower for PR and NR response categories, although survival for VGPR responses appear well aligned.
        - At six months, the unadjusted EMN23-UK and ALchemy curves are more closely aligned with the exception of the NR response category where the ALchemy dataset indicates higher survival.

- Without access to IPD from ALchemy, Janssen has been unable to investigate these differences further. However, as documented in the 'Summary of key appeal outcomes and their impact' section above, clinical expert opinion at the appeal hearing supported the use of the recategorized EMN23-UK dataset over ALchemy. Janssen consider it important to note that the re-categorised EMN23-UK dataset adjusts for confounding from treatment switching and uses response categorisation that is representative of clinical practice, whereas the ALchemy and unadjusted EMN23-UK datasets do not.
- Extrapolation curves have not been fitted to the KM data as per the request from NICE given the limited timeframe to submit this response addendum.

b) KM curves of overall survival at three and six months based on the unadjusted EMN23-UK dataset (i.e., before re-categorisation to align with response criteria in ANDROMEDA), compared with the unadjusted EMN23-UK data with the patients with missing data for re-categorisation removed. In the absence of individual patient data, the KM data from each source were first digitised using software and the Guyot algorithm then used to produce pseudo-IPD to compare outcomes on the same plot.

- KM curves for overall survival stratified by response category based on the unadjusted EMN23-UK data *excluding* the missing patients and unadjusted EMN23-UK data *prior to* exclusion of missing patients are presented in Figure 9**Error! Reference source not found.** and Figure 10 (three months and six months, respectively).
- These graphs demonstrate a considerable similarity, and commonly overlap, between the adjusted and unadjusted data, providing strong evidence that the impact of excluding patients with missing data for re-categorisation is negligible.
- As above, extrapolation curves have not been fitted to the KM data as per the request from NICE, since the presented digitised KM data illustrate the comparability between datasets well, and given the limited timeframe to submit this response addendum.

c) Additional information or analysis on the missing data in EMN23-UK dataset

- To further investigate the impact of missing data in the EMN23-UK dataset, Janssen followed-up with the EMN study group to obtain a reconciliation of UK patient numbers included in the OS analysis with re-evaluated responses.
- The reconciliation of EMN23-UK patients at three and six months is presented in Table 6. The majority of 'missing' patients not available for re-evaluation of response died prior to the landmark assessment timepoint and have been correctly excluded from the re-categorised analysis ([redacted] and [redacted] patients at three and six months respectively). The number of true missing patients due to laboratory test data not being available was [redacted] and [redacted] patients at three and six months respectively, representing approximately [redacted] of the EMN23-UK patients available for landmark analysis.
- Janssen consider that the impact of true missing data due to missing laboratory data on the re-evaluated responses from the EMN23-UK dataset is likely to be minimal which is supported by visual inspection of the KM charts presented in Figure 9 and Figure 10 of the Appendix.

- Overall, as expected, it can be concluded that the OS data from the UK cohort of the EMN23 study prior to response re-categorisation broadly align with OS data from the ALchemy study, and furthermore that the patients missing from the UK cohort of the EMN23 response re-categorisation process have minimal impact on OS results.

Conclusions

- The results of the revised economic analyses presented herein illustrate that DBCd represents a cost-effective use of NHS resources, particularly given the rare nature and substantial unmet need associated with this condition.
- The additional evidence requested by NICE illustrates that the OS data from the UK cohort of the EMN23 study prior to response re-classification broadly aligns with OS data from the ALchemy study, and furthermore that the true number of missing patients from the EMN23 response re-classification was minimal (~5%) and unlikely to bias the results.
- Should a recommendation be made for routine commissioning, DBCd will fulfil a substantial unmet need for newly diagnosed AL amyloidosis patients, for whom no licenced treatments are currently recommended by NICE.
- However, should the NICE committee consider that further evidence collection for DBCd is required, Janssen maintain that patient access via the CDF is a valid alternative route.

Appendix

Response deepening and maintenance over time

The deepening of response over time in AL amyloidosis patients receiving DBCd treatment is supported by the results of the ANDROMEDA trial. As presented in Table 4 (which is a reproduction of Table 1 of Janssen's response to Technical Engagement), although the proportion of patients in the DBCd arm achieving a VGPR or better (VGPR or CHR) or any overall response (CHR, VGPR or PR) remained approximately stable between the IA1 and 12-month landmark analyses, CHR rates in the DBCd arm rose and VGPR rates fell between these data cuts, evidencing an overall deepening of response from VGPR to CHR with time on DBCd therapy.

Furthermore, as presented in Table 5 (which is a reproduction of Table 14 in Appendix 3 of Janssen's ACD response document), [redacted] patients ([redacted]) in the DBCd arm who achieved a CHR at Month 3 sustained it to Month 24, as compared with [redacted] patients ([redacted]) in the BCd arm. Considering CHR achievement at Month 6, CHR maintenance rates at Month 24 were [redacted] ([redacted] patients) versus [redacted] ([redacted] patients) in the DBCd and BCd arms, respectively.

Together, these data demonstrate that daratumumab maintenance helps to deepen a patient's initial response to treatment and sustain responses for longer.

Table 4: Summary of overall best confirmed haematologic response based on IRC assessment; ANDROMEDA ITT analysis set (14th February 2020 data cut-off and 13th November 2020 data cut-off)

Response	IA1, % (95% CI[a])		12-month landmark, % (95% CI[a])	
	BCd (N=193)	DBCd (N=195)	BCd (N=193)	DBCd (N=195)
CHR	18.1 (13.0, 24.3)	53.3 (46.1, 60.5)	19.2 [redacted]	59.0 [redacted]
VGPR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
NE	[redacted]	[redacted]	[redacted]	[redacted]
VGPR or better (CHR+VGPR)	49.2 [redacted]	78.5 [redacted]	50.3 [redacted]	79.0 [redacted]
Overall response[b]	76.7 [redacted]	91.8 [redacted]	76.7 [redacted]	91.8 [redacted]

[a] 95% CIs are based on Clopper-Pearson exact test. [b] Overall response defined as CHR+VGPR+PR.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CHR: complete haematologic response; CI: confidence interval; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; IA1: Interim Analysis 1; ITT: intention-to-treat; NE: not evaluable; NR: no response; PD: progressive disease; VGPR: very good partial response.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[25] Kastritis *et al.,* (2020);[26] Janssen ANDROMEDA 12-month landmark analysis (2021);[27] Kastritis *et al.,* (2021).[28]

Table 5: Sustained response in subsequent months observed in patients achieving CR at 3 months and 6 months per treatment arm. ANDROMEDA, May 2021 data cut-off (18-month landmark analysis)

CR at 3 months	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24	%
DBCd																							
CR	[redacted]																						[redacted]
Total	[redacted]																						
BCd																							
CR	[redacted]																						[redacted]
Total	[redacted]																						
CR at 6 months	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**	**M14**	**M15**	**M16**	**M17**	**M18**	**M19**	**M20**	**M21**	**M22**	**M23**	**M24**	
DBCd																							
CR				[redacted]																			[redacted]
Total				[redacted]																			
BCd																							
CR				[redacted]																			[redacted]
Total				[redacted]																			

Abbreviations: CR: complete hematologic response; VGPR: very good partial response; PR: partial response; NR: no response; PD: progressive disease; M1–M24: Month 1 to Month 24; NE: not estimated.

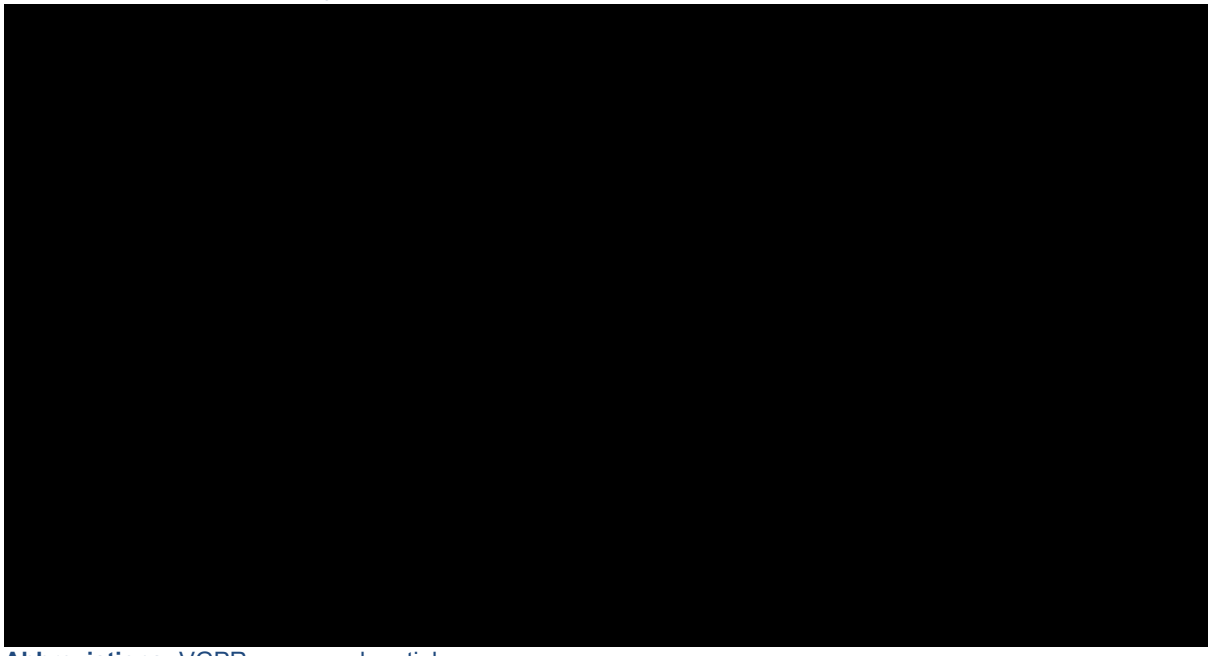
NICE request 2: EMN23-UK dataset and missing data

a) Kaplan-Meier (KM) curves of overall survival at three and six months based on the original EMN23 dataset, the unadjusted EMN23-UK dataset (i.e., before re-categorisation to align with response criteria in ANDROMEDA), compared to the ALchemy dataset.

Figure 1: Overall survival for patients achieving CR in the original EMN23, unadjusted EMN23-UK and ALchemy cohorts at three months

Abbreviations: CR: complete response.

Figure 2: Overall survival for patients achieving VGPR in the original EMN23, unadjusted EMN23-UK and ALchemy cohorts at three months



Abbreviations: VGPR: very good partial response.

Figure 3: Overall survival for patients achieving PR in the original EMN23, unadjusted EMN23-UK and ALchemy cohorts at three months

Abbreviations: PR: partial response.

Figure 4: Overall survival for patients achieving NR in the original EMN23, unadjusted EMN23-UK and ALchemy cohorts at three months

Abbreviations: NR: no response.

Figure 5: Overall survival for patients achieving CR in the original EMN23, unadjusted EMN23-UK and ALchemy cohorts at six months

Abbreviations: CR: complete response.

Figure 6: Overall survival for patients achieving VGPR in the original EMN23, unadjusted EMN23-UK and ALchemy cohorts at six months

Abbreviations: VGPR: very good partial response.

Figure 7: Overall survival for patients achieving PR in the original EMN23, unadjusted EMN23-UK and ALchemy cohorts at six months

Abbreviations: PR: partial response.

Figure 8: Overall survival for patients achieving NR in the original EMN23, unadjusted EMN23-UK and ALchemy cohorts at six months

Abbreviations: NR: no response.

b) KM curves of overall survival at three and six months based on the unadjusted EMN23-UK dataset (i.e., before re-categorisation to align with response criteria in ANDROMEDA), compared with the unadjusted EMN23-UK data with the patients with missing data for re-categorisation removed.

Figure 9: Overall survival for patients in the unadjusted EMN23-UK dataset (before re-categorisation to align with response criteria in ANDROMEDA) and unadjusted EMN23-UK with the patients with missing data for re-categorisation removed cohorts at three months

Abbreviations: CR: complete response; NR: no response; PR: partial response; VGPR: very good partial response.

Figure 10: Overall survival for patients in the unadjusted EMN23-UK dataset (before re-categorisation to align with response criteria in ANDROMEDA) and unadjusted EMN23-UK with the patients with missing data for re-categorisation removed cohorts at six months

Abbreviations: CR: complete response; NR: no response; PR: partial response; VGPR: very good partial response.

Note: the original analysis for the EMN23 study reported best response until the 3- and 6-month landmark assessment timepoint. This meant that patients that died prior to the landmark assessment timepoints were included in the analysis. The clear separation and upward shift for the NR response category in Figure 10 when missing data is excluded is largely attributable to the exclusion of patients that died prior to the landmark assessment timepoint.

c) Additional information or analysis on the missing data in EMN23-UK dataset

Table 6: Reconciliation of patients included in re-evaluated EMN23-UK OS by response analysis

	3-month landmark assessment	6-month landmark assessment
All UK patient, post 2010	[redacted]	[redacted]
Death prior to landmark assessment timepoint	[redacted]	[redacted]
All UK patients, post 2010 available for landmark analysis	[redacted]	[redacted]
Exclusions		
Patients that switched treatment prior to 3m/ 6m	[redacted]	[redacted]
NA lab data	[redacted]	[redacted]
Response (ANDROMEDA re-evaluated) available UK data	[redacted]	[redacted]
Missing OS data	[redacted]	[redacted]
Patients included in OS with ANDROMEDA re-evaluated responses	[redacted]	[redacted]

Abbreviations: m: month; NA: not available; OS: overall survival.

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Statement from Myeloma UK following the appeal against the final appraisal determination for daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Myeloma UK appealed against NICE's Final Appraisal Determination [ID3748] not to recommend daratumumab in combination for untreated systemic amyloid light-chain amyloidosis on four grounds.

The appeal was upheld, and a third committee meeting scheduled to discuss and address the appeal panel's recommendations.

Whilst we understand that the Committee is not looking for new evidence and will only be examining specific points as instructed by the appeals panel during the third committee meeting, we wanted to take the opportunity to provide a brief summary of our appeal points and how we as appellants feel the points could be addressed during the meeting.

Gound 1a.1 has failed to act fairly by not taking into account the advice and experience of haematologists at every stage of the appraisal process and Ground 1a.2 NICE has not acted fairly by failing to allow the National Amyloidosis Centre to nominate its clinical expert for committee meetings.

AL amyloidosis is a rare, complex, and very individual condition. Patients are treated by several clinicians, including haematologists, cardiologists, and nephrologists, depending on the organs affected by the disease. However, as a plasma cell dyscrasia, it is classed as a haematological condition. Haematologists are the treating physicians for all AL amyloidosis patients, taking the lead on treatment decisions. They are the most relevant clinicians to comment on treatment, treatment response and clinical practice in AL amyloidosis.

However, NICE did not invite a haematologist to submit written evidence during the appraisal process or attend the first committee meeting. As a result, expert testimony from haematologists was not available to Committee members.

Whilst we are pleased that both Dr Mamta Garg and Professor Ashutosh Wechalekar have been invited to the third committee meeting it is vital that the Committee give them sufficient opportunity to provide expert testimony and opinion on the evidence presented by the company and evidence reference group.

We believe it is particularly important that the Committee hear their expert opinion on the measurement and categorisation of haematological response. The haematologists can help confirm the current gold standard for defining complete response, how this definition compares to the criteria used in the ANDROMEDA trial, the ALchemy study, and the EMN23-UK data and how the differences in the criteria used impact the overall survival extrapolations.

The Committee should also seek their expert opinion the validity of overall survival extrapolations presented by both the company and the ERG. The UK data used in each study comes from the NAC registry, and, therefore, Professor Ashutosh Wechalekar is uniquely qualified to comment on the strength and plausibility of the datasets.

Myeloma UK believes this valuable testimony is required to ensure NICE has acted fairly in their appraisal of this treatment.

1(a).4 NICE has failed to act fairly when applying the criteria for determining an acceptable ICER value under the Methods Guide 2013

Myeloma UK felt that the Committee's decision that an acceptable ICER is £20,000 per QALY gained because of the uncertainty was unfair.

The explanation for the decision, as outlined in the FAD section 3.20, only mentions how uncertainty has impacted this decision but not how the rarity, severity of the disease or the quality-of-life benefits of the treatment influenced their decision regarding the ICER threshold.

Whilst there is uncertainty around the size of the overall survival benefit, it is clear that daratumumab delivers significant health benefits to patients. In section 3.7 of the FAD, the Committee concluded that daratumumab improves haematological response and reduces major organ deterioration. Both outcomes are significant for patients and their families, improving their physical and psychological well-being. You can read more about these benefits in the statement provided by AL amyloidosis patient Michael Jameson at the appeal hearing.

Myeloma UK believes the Committee should reflect on the rarity of AL amyloidosis and the significant treatment benefits when reviewing their decision regarding the ICER threshold.

Ground 2.1 (The Appraisal Committee's conclusion that "both ALchemy and EMN23-UK may be representative of UK clinical practice" is unreasonable in light of the evidence submitted) as far as this relates to ALchemy only.

Myeloma UK felt the Committee's conclusion that the ALchemy data "may be representative of UK clinical practice" and that the extrapolated overall survival "may lie between the Alchemy data and the censored and re-categorised EMN23-UK data" was unreasonable. We believe the overall survival extrapolations from ALchemy data should either be discounted or given little weight. The analyses from the ALchemy data cannot be accurate or representative when it has not been recategorized to reflect the internationally agreed criteria for complete haematological response.

We believe The Committee should discuss and review the overall survival extrapolations considering the expert opinions of the haematologists invited to the third committee. They are uniquely qualified to provide perspective on the accuracy and validity of the overall survival extrapolations from the EMN23-UK and ALchemy datasets.

Personal Statement given by AL amyloidosis patient Michael Jameson as a Myeloma UK representative at the appeal hearing.

Good morning. My name is Michael Jameson, I'm 42 years old and I live in Walsall in the West Midlands with my Wife, Kathrine and two children, Grace who is 10 and Emily who is 6. I've been asked here today to tell you my experience of being treated with Daratumumab.

My symptoms first began in September of 2021. Having experienced pain in my chest and left arm I was admitted to my local hospital for what was initially a suspected heart attack. After 4 weeks in hospital and multiple tests I was discharged with a diagnosis of Myocarditis, an inflammation of the heart and given a 6-week rehabilitation program to follow. However, during these 6 weeks my condition deteriorated further, and I started to suffer with nausea and vomiting on top of my existing symptoms. At the end of Nov 21 my symptoms were so severe that I was readmitted to hospital and subject to another MRI scan which identified that the inflammation of my heart had become worse. The local cardiologists were at a loss as to what was causing my sickness and heart symptoms but were going to quote 'throw the book at me' in order to find out. After a further 3 weeks of inpatient stay and investigations I was not in a good condition. I was physically drained of all energy and practically bed bound. Due to the vomiting and lack of activity I had lost over 4 stone in weight since I initially became symptomatic, and I was now struggling with everyday tasks. My mobility was severely impacted, and I was reliant on a wheelchair. Then in late December, one of my cardiologists finally suggested the possibility of Amyloidosis, a rare protein condition which can impact the heart and other organs. I was referred to the National Amyloidosis Centre in London to undergo further testing.

On the 23rd of December 2021, following two days of testing at the NAC, I was finally diagnosed with kappa light chain multiple myeloma and stage 3b systemic AL Amyloidosis, with advanced cardiac involvement and additional liver, spleen, and gut involvement. My kappa light chain levels, a key marker for Myeloma and AL Amyloidosis were over 2000, where a normal person would be expected to be around 20. In addition, my NT proBNP levels, a key marker of heart distress, was over 30000 with anything over 100 being abnormal and an indication of heart failure. I was given a nominal life expectancy of 3 months which, for a 41-year-old man with 2 young children, was devastating not only for myself but also my family. My consultant advised I needed immediate treatment but that the most effective treatment was only available to private patients. Fortunately, I had Bupa health cover through my employer, and I was scheduled in to attend as an inpatient at a private hospital in London.

I was admitted to HCA at UCLH on the 29th of December where I was started on a regime of Daratumumab with methylprednisolone. Due to my dangerously low blood pressure, it was decided not to give me Cyclophosphamide and Bortezomib at first. My response to the Daratumumab was immediate and blood results would show that my kappa light chain levels had dropped by 50% after just the first dose. However, I was still dangerously unwell and needed ongoing monitoring and inpatient stay. The following week I would receive the full suite of drugs. This resulted in a further 50% reduction in kappa light chain levels being observed but I was less tolerant of the bortezomib, and my blood pressure dropped dangerously low. For the third week the level of bortezomib was altered resulting in the same pattern of kappa light chain reduction and it was decided that I could be discharged and would return weekly for ongoing treatment. At the point of discharge my kappa light chain levels were 189 and my NT proBNP had dropped to 16000.

Although I was far from being well again, I was at least stable as I began my weekly routine of travelling to London for treatment. Side effects such as fluid retention, nausea, vomiting and low blood pressure were common each week, but the improvements continued despite contracting COVID and having to have a six-week treatment break. By the end of April 22, light chains were 91. At this point I was now walking small amounts and less reliant on the wheelchair. I was more able to complete everyday tasks at home.

By June 22, light chains had dropped to 57 and NT proBNP was down to 12000. I was no longer using a wheelchair and I was becoming more and more self-sufficient.

In September 22, I was well enough to take a family holiday and then, at the end of the month, I was able to get married. In November 22, I was able to start making a phased return to work.

Now I am back in full time employment, I am attending regular exercise sessions to improve my heart health in preparation for my stem cell transplant. My kappa light chain levels are now stable at 31 and NT proBNP is down to 1500. This puts me at a very good partial response (VGPR) to treatment and almost a

complete response (CR). I find it remarkable to see where I started to where I am today thanks to daratumumab, and I am grateful that this treatment was available to me. Hopefully by telling my story, you will also see how important it is that this treatment should be made available to all systemic amyloidosis patients.

Thank you.

Single Technology Appraisal (STA)

Daratumumab in combination for newly diagnosed systemic amyloid light-chain amyloidosis [ID3748]

ERG addendum 2: review of company's post-appeal submission addendum

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Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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1 Overview

This second addendum to the Evidence Review Group (ERG) report presents the ERG's critique of the additional evidence provided by the company in their submission addendum following publication of the appeal decision.

The company's addendum presented new evidence or analyses for five issues. A new PAS was also provided along with new results from the cost-effectiveness analysis. The ERG review of the company's addendum is presented in Section 2. The results of the company and ERG's updated analyses are presented in Section 3.

2 Description and critique of additional evidence

2.1 Relationship between haematologic response and key clinical outcomes

The company provided additional evidence relating to the relationship between haematologic response, major organ deterioration and overall survival. This addressed two related issues: (1) the prognostic utility of haematologic response for overall survival (OS) in patients with newly diagnosed AL amyloidosis, and (2) the risk of confounding in the relationship between haematologic response and OS.

In relation to (1), the company cited a recent meta-analysis of nine observational studies that indicated a strong relationship between achievement of complete response (CR) or very good partial response (VGPR) and improved OS (HR 0.21 [95% CI 0.13–0.34] and HR 0.21 [95% CI 0.17–0.26] respectively).[1] They also noted the findings of a sensitivity analysis showing that patients achieving CR showed better OS than those achieving VGPR (four studies; HR point estimates ranging from 0.24 to 0.72). The company noted that the conclusion of this meta-analysis meets Level 2 of evidence for surrogate relationships as defined in Section 4.6.6 of the NICE Process and Methods Manual i.e. a biologically plausible relationship supported by a consistent association between surrogate endpoint and final outcomes derived from epidemiological or observational studies.[2]

In relation to (2), the company noted that they originally conducted a multivariate analysis to explore confounding in the relationship between haematologic response and OS in response to the ACD. However, due to the relatively small sample size and few events available from the interim ANDROMEDA data cut, the model failed to converge and was therefore uninformative. The company added that in the absence of a new data cut, this analysis cannot currently be updated.

2.1.1 ERG's critique

The ERG considers it to be widely accepted that the goal of treatment in systemic AL amyloidosis is to reduce native light-chain production and its associated organ toxicity, subsequently reducing

mortality caused by impaired organ function. The ERG agrees that the relationship between deep haematologic response and improved OS is both biologically plausible and supported by the evidence.

The potential risk of confounding in the observed relationship between haematologic response and OS in ANDROMEDA was initially raised during the first committee meeting. As noted by the ERG at the time, the company's original multivariate analysis to explore this question produced uninformative results. The ERG accepts that this was due to the limited data available from the ANDROMEDA trial, and that no new trial data is currently available to update the multivariate analysis. The company has not provided new evidence to address this issue.

2.2 Use EMN23-UK dataset

Following the first committee meeting, the company decided to use the EMN23-UK cohort data instead of ALchemy (a UK cohort, expressed as committee preference), due to the need to re-classify haematologic response using current criteria used in the UK and to match the criteria used in the ANDROMEDA trial. In response to the ACD consultation, the ERG noted that in principle the EMN23-UK cohort was a suitable alternative to using the ALchemy data because of the very high (~95%) level of overlap in participants between the two UK cohorts. We would therefore expect near equivalent outcomes for these two cohorts, given that the ALchemy and the original unadjusted EMN23-UK cohort include essentially the same data from the same participants. However, the ERG was unable to confirm whether outcomes were near equivalent between the two data sources, because the original unadjusted data for the UK-only EMN23 cohort were not presented by the company for comparison to the ALchemy data. In the Appendix to their addendum, the company have now provided Kaplan-Meier (KM) curves for OS at three and six months based on the original EMN23 dataset, the unadjusted EMN23-UK dataset (i.e., before re-categorisation), and the ALchemy dataset for patients achieving CR, VGPR, partial response (PR) and no response (NR) (Figures 1 to 8, Appendix to company's addendum). Extrapolation of these curves was not presented.

The company have also not presented a comparison of the haematologic response rates at the three and six-month assessment time points for the unadjusted EMN23-UK cohort data with ALchemy or ANDROMEDA and the re-categorised EMN23-UK data.

2.2.1 ERG's critique

The ERG considers the comparison between the OS curves for the unadjusted EMN23-UK dataset and the ALchemy dataset to be the most relevant – Figures 1 to 8 of the Appendix to the company's addendum. To provide reassurance that the EMN23-UK dataset is indeed similar to ALchemy before re-categorisation of the response criteria, the ERG would expect to see KM curves with a substantial overlap, perhaps with the exception of the very final part of the curves where fewer patients are contributing, and small divergences might be expected.

As acknowledged by the company, overall survival for patients achieving CR at three months in ALchemy is noticeably higher relative to the unadjusted EMN23-UK cohort data (Figure 1, Appendix to company's addendum) but lower for PR and NR response categories (Figures 3 and 4, Appendix to company's addendum). Although overall survival for VGPR appears well aligned up to 35 months (Figure 2, Appendix to company's addendum), there appears to be some divergence beyond this, with higher survival in ALchemy up to around 60 months. For the same comparison at six-months, the ALchemy survival is noticeably higher relative to EMN23-UK for CR and NR, and during the ~35-60 month period for VGPR (Figures 5, 8 and 6, Appendix to company's addendum, respectively). However, for PR, survival is higher in EMN23-UK until 35 months (Figure 7, Appendix to company's addendum).

These differences are greater than might be expected for ~95% level of overlap in participants between the two UK cohorts and do not provide reassurance to the ERG that the overall survival curves from the two datasets are equivalent. In fact, in some cases the ALchemy OS curves are closer to the full EMN23 dataset (which included non-UK patients) than to the EMN23-UK only OS curves. The company were unable to investigate the reasons for these apparent differences. Without access to data from either study, or knowledge of the procedures by which ALchemy data were incorporated into the full EMN23 study and then UK patients selected to form EMN23-UK, the ERG cannot comment on the reasons for the observed differences in overall survival between EMN23-UK and ALchemy cohort data. However, given the importance of the overall survival outcomes on the cost-effectiveness results, this unexplained discrepancy is concerning.

2.3 Re-categorisation of EMN23-UK to align with response criteria in ANDROMEDA

Following the first committee meeting, the EMN23-UK data were re-classified using current criteria used in the UK to assess haematologic response. Whilst the ERG were satisfied with the general principles of the re-classification approach undertaken by the company, this process led to a substantial loss of participant data due to missing laboratory data. On the basis of missing laboratory data alone, 205 out of an initial 1,155 participants (18%) were excluded from the three-month haematologic response analysis, and 228 out of an initial 1,052 participants (22%) were excluded from the six-month response analysis. Although the ERG agreed that the reclassification of response was important and it was plausible that data were missing at random, no analyses were conducted to allow this to be checked by the ERG.

In Table 6 of the company's addendum appendix, the company reported the reasons for data being missing from the re-classification. Excluding patients who died prior to the landmark assessment timepoint or switched treatment prior to assessment, the number of true missing patients due to laboratory test data not being available was [redacted] and [redacted] patients at three and six months respectively, representing approximately [redacted] of the EMN23-UK patients available for landmark analysis.

Figures 9 and 10 of the company's addendum appendix compare overall survival curves for the unadjusted EMN23-UK dataset with and without the patients with missing data for recategorization. The company concluded that these graphs demonstrate a considerable similarity, and overlap, between the adjusted and unadjusted data, providing strong evidence that the impact of excluding patients with missing data for re-categorisation is negligible.

2.3.1 ERG's critique

The ERG is reassured by the additional information provided in the addendum, and agrees that the true proportion of patients missing laboratory test data is low and the impact of excluding these patients from the reclassification is likely to be negligible.

2.4 Survival benefit associated with daratumumab maintenance therapy

In the FAD, the committee concluded that the company's approach to modelling an expected survival benefit for daratumumab maintenance therapy was not appropriate. In the model the company had uplifted the per-cycle survival probabilities for all haematologic response categories in the DBCd treatment arm from cycle 7 onwards by a factor of 1.044, indicating a 4.4% higher survival benefit associated with daratumumab maintenance therapy. The factor of 1.044 was based on the difference between the observed ratio of surviving patients from ANDROMEDA at a median follow-up of 20.3 months for DBCd versus BCd (1.066) and the equivalent ratio from the re-categorised EMN23-UK cohort data (1.021). The committee noted that applying this benefit independent of haematologic response categories was unlikely to be appropriate.

Following the appeal hearing, the company have revised their approach to take into consideration the committee's concerns. The company have implemented the survival benefit associated with daratumumab maintenance therapy from cycle 7 onwards by applying the 4.4% efficacy uplift to the CR and VGPR categories *only*, rather than all response categories, because they believe that this represents an important unquantified benefit of daratumumab maintenance treatment.

2.4.1 ERG's critique

The ERG considers the application of the efficacy uplift to only the CR and VGPR response categories to be more appropriate than application to all response categories. The ERG notes that this is implemented as a long-term survival benefit, even after daratumumab maintenance monotherapy is stopped at a maximum of 24 cycles. The company support this based on the deeper and more durable responses observed for CR maintenance to month 24 for DBCd versus BCd arms in ANDROMEDA (Table 1 of the company's addendum). The implementation in the model is correct.

2.5 New administration costs included in the economic model

The company updated the administration costs for bortezomib and daratumumab in line with the committee preferred assumptions presented in the FAD, i.e., an increase in chemotherapy administration costs to £1,127 per cycle applied to both daratumumab in combination and standard care arms for cycles 1 to 6, and £161 per cycle for daratumumab maintenance monotherapy from cycle 7 onwards.

2.5.1 ERG's critique

The ERG considers the company's approach to be appropriate and the implementation in the model is correct for first line therapies. The ERG notes that the administration cost of £161 for first cycle and £322 for subsequent cycles (based on HRG code SB15Z) is not included for subcutaneous administration of second line therapies (9% on BORT/CYC/DEX); however, the implications for the cost-effectiveness results are very minor and conservative towards daratumumab (decreases the company's revised base case ICER by £42).

3 Results

3.1 Company revised base case and scenario analyses

The company presents results of a revised base case and scenario analyses following the FAD. The assumptions in the company's revised base-case are summarised as follows:

- Inclusion of an updated Patient Access Scheme (PAS) for daratumumab of [redacted] on the list price [redacted].
- The distribution of haematologic response for BCd is based on the re-categorised EMN23-UK cohort data and relative effectiveness for DBCd informed by ANDROMEDA.
- Haematologic response is assessed at 3 months.
- Extrapolated overall survival by haematologic response is based on the re-categorised EMN23-UK cohort data.
- An increased relative survival benefit of 4.4% for DBCd compared to BCd has been applied by uplifting the per-cycle survival probabilities for CR and VGPR in the DBCd treatment arm from cycle 7 onwards by a factor of 1.044.
- The chemotherapy administration costs are £1,127 per cycle applied to both daratumumab in combination and standard care arms for cycles 1 to 6, and £161 per cycle for daratumumab maintenance monotherapy from cycle 7 onwards.

The company conducts four scenario analyses, where the base-case assumptions hold except for the following changes:

- Scenario 1: No additional survival benefit associated with daratumumab monotherapy (i.e., removing the uplift of 4.4% for CR and VGPR).
- Scenario 2: The haematologic response is assessed at 6 months rather than 3 months.
- Scenario 3: Combination of scenarios 1 and 2 (i.e., no additional survival benefit associated with daratumumab monotherapy and haematologic response assessed at 6 months).
- Scenario 4: Health state utility values derived from UK clinician estimations at an advisory board as per Section B.3.4.1 of the company's original submission.

The results of the company's revised base-case and scenario analyses are shown in Table 1 and Table 2, respectively.

Table 1 Company's revised base-case results following the FAD

Treatment	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
BCd	74,087	4.21			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	23,321

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 2 Results of the company's scenario analyses following the FAD

Treatment	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Scenario 1: No additional survival benefit associated with daratumumab monotherapy					
BCd	74,087	4.21			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	25,537
Scenario 2: 6-month haematologic response assessment					
BCd	68,904	4.15			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	22,398
Scenario 3: Scenario 1 + 2					
BCd	68,904	4.15			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	24,442
Scenario 4: Health state utility values derived from UK clinician estimations					
BCd	74,087	3.70			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	17,510

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; AC, Appraisal Committee.

A confidential appendix to this addendum presents the results of the company's revised base case and scenario analyses when the confidential PAS discounts and Commercial Medicine Unit (CMU) procurement prices are applied for daratumumab, bortezomib, the relevant concomitant therapies, and the relevant subsequent therapies used to calculate the costs of second- and third-line therapies in the model.

3.2 Critique of the company's revised base case and scenario analyses

A comparison of the company's revised base-case assumptions and the committee's preferred assumptions (as outlined in Section 3.21 of the FAD) is presented in Table 3 below.

Table 3 Comparison of committee and company preferred assumptions

Committee preferred assumption	Company's revised analyses	ERG comment
To include people with end-stage cardiac and renal disease in the population	Yes	The primary source of data for standard of care is the EMN23-UK cohort which includes people with end-stage cardiac and renal disease.
That the distribution of haematologic response for standard care may lie between ALchemy and the censored and re-categorised EMN23-UK	Partially	The company consider the re-categorised EMN23-UK cohort data as the only data source suitable for representing outcomes with standard of care in the UK.
That there may be confounding factors in the relationship between haematologic response and overall survival	Partially	The company argue that there is a substantial body of evidence supporting the prognostic relationship between depth of haematologic response and improved overall survival in patients with newly diagnosed AL amyloidosis.
To assess haematologic response at 3 months in the base case but explore a scenario using 6 months	Yes	The company have assessed haematologic response at 3 months in the base case and at 6 months in a scenario analysis.
That the extrapolated overall survival in the longer term may lie between the ALchemy data and the censored and re-categorised EMN23-UK data	Partially	The company have used the re-categorised EMN23-UK cohort data as an alternative to ALchemy for the extrapolation of overall survival by haematologic response.
That the company's approach of applying an expected increased survival benefit for daratumumab maintenance monotherapy is not appropriate for decision making	Yes	The company have included an additional survival benefit for daratumumab maintenance monotherapy to the CR and VGPR response categories only, in the base case analysis. This is excluded in a scenario analysis.
That some utility data lack face validity	**No**	The company present a scenario with health state utility values derived from UK clinicians but as critiqued in the EAG report these are not relevant for decision making.
To apply a stopping rule for daratumumab monotherapy of a maximum of 24 cycles	Yes	Daratumumab is given for a maximum of 24 cycles.
To increase chemotherapy administration costs to £1,127 per cycle applied to both daratumumab in combination and standard care arms for cycles 1 to 6, then £161 per cycle for daratumumab maintenance monotherapy from cycle 7 onwards	Yes	The company have updated the chemotherapy administration costs in their revised base case.

The effect of the company's revised changes to the committee's preference following the FAD is shown in Table 4.

The ERG considers the company's scenario analyses 1 to 3 relevant for decision making, but not scenario 4 using health state utility values derived from UK clinicians. The use of health state utility

values from clinicians, rather than EQ-5D data, was critiqued in the ERG report (please refer to Section 4.2.8.2 of the ERG report). No new information has been provided in the company's addendum for the ERG to revise their position on these data.

The committee considered assessment of haematologic response at 6 months to be explored in a scenario. Therefore, Table 5 presents the effect of the company's revised changes to the committee preference following the FAD with haematologic response assessed at 6 months.

A confidential appendix to this addendum presents the results of the committee preference following the FAD when the confidential PAS discounts and CMU procurement prices are applied for daratumumab, bortezomib, the relevant concomitant therapies, and the relevant subsequent therapies used to calculate the costs of second- and third-line therapies in the model.

Table 4 Effect of the company's revised changes to the committee preference following the FAD (base case analysis with haematologic response assessed at 3 months)

Scenario	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
Re-categorised EMN23-UK cohort data						
Committee preferred assumptions using the re-categorised EMN23-UK cohort data for distribution of haematologic response for BCd at 3 months and extrapolated overall survival, with updated PAS discount for daratumub	BCd	£ 74,087	4.21			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 25,537
+ additional relative survival benefit of 4.4% for DBCd compared to BCd in maintenance phase with daratumumab monotherapy, applied to CR and VGPR categories only (Company revised base case)	BCd	£ 74,087	4.21			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 23,321
ALchemy data						
Committee preferred assumptions using ALchemy for distribution of haematologic response for BCd at 3 months and extrapolated overall survival, with updated PAS discount for daratumub	BCd	£ 68,355	4.04			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 38,797
+ additional relative survival benefit of 4.4% for DBCd compared to BCd in maintenance phase with daratumumab monotherapy, applied to CR and VGPR categories only	BCd	£ 68,355	4.04			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 33,448

Table 5 Effect of the company's revised changes to the committee preference following the FAD for scenario analysis with haematologic response assessed at 6 months

Scenario	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
Re-categorised EMN23-UK cohort data						
Committee preferred assumptions using the re-categorised EMN23-UK cohort data for distribution of haematologic response for BCd at 6 months and extrapolated overall survival, with updated PAS discount for daratumub	BCd	£ 68,904	4.15			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 24,442
+ additional relative survival benefit of 4.4% for DBCd compared to BCd in maintenance phase with daratumumab monotherapy, applied to CR and VGPR categories only	BCd	£ 68,904	4.15			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 22,398
ALchemy data						
Committee preferred assumptions using ALchemy for distribution of haematologic response for BCd at 6 months and extrapolated overall survival, with updated PAS discount for daratumub	BCd	£ 63,596	3.93			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 35,311
+ additional relative survival benefit of 4.4% for DBCd compared to BCd in maintenance phase with daratumumab monotherapy, applied to CR and VGPR categories only	BCd	£ 63,596	3.93			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 30,815

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